

Inverse Relationship Between Education and Parietotemporal Perfusion Deficit in Alzheimer's Disease

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A higher prevalence of dementia in individuals with fewer years of education has suggested that education may protect against Alzheimer's disease (AD). We tested whether individuals with more years of education have a more advanced AD before it is clinically evident. As a measure of pathophysiological severity, we quantified regional cerebral blood flow (rCBF), by the $^{133}\text{Xenon}$ inhalation technique; a specific pattern of flow reduction in the parietotemporal cortex corresponds to AD pathology. In 3 groups of patients with probable AD, matched for clinical measures of dementia severity but with varying levels of education, whole-cortex mean flows were comparable. However, the parietotemporal perfusion deficit was significantly greater in the group with the highest level of education, indicating that AD was more advanced in this group. We conclude that education or its covariates or both may provide a reserve that compensates for the neuropathological changes of AD and delays the onset of its clinical manifestations.

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The relationship between education and dementia is controversial. Several epidemiological studies report a higher prevalence of Alzheimer's disease (AD) in individuals with fewer years of education [1]. One interpretation of these findings has been that education represents a confound; individuals with lower educational levels perform more poorly on screening tests for dementia, which results in a higher rate of detection. This in turn introduces high false-positive rates in individuals with low education and high false-negative rates in those with more education [2]. A second interpretation is that the prevalence of AD in the higher education ranges may actually be lower, indicating protection [3, 4].

A hypothesis that supports this second interpretation is tested in the present study; that is, education may actually provide a reserve that must be depleted to a certain threshold before dementia is clinically manifest and in that sense it protects against the emergence of the clinical features of AD. If this is the case, we would predict that years of education would correlate inversely with degree of AD pathology, given comparable clinical severity of dementia. To evaluate the degree of AD pathology, we used regional cerebral blood flow (rCBF), assessed with the $^{133}\text{Xenon}$ inhalation method. Using both rCBF and positron emission to-

mographic scanning, a characteristic parietotemporal perfusion and metabolic deficit has been demonstrated in patients with AD [5-8]. This pattern of flow reduction is sensitive and specific, as follows: (1) It is well correlated in AD patients with postmortem histological diagnosis [9]. (2) It is present from the early stages of disease [10]. (3) It discriminates AD from major depressive disorder, multiinfarct dementia, Pick's disease, and normal aging [11-14]. And (4) it correlates with disease severity and increases with disease progression [7]. Postmortem studies have also shown the maximal histopathology in similar parietotemporal areas [15].

If advanced education increases the threshold for detecting the clinical manifestations of AD, then more severe pathological changes would be present in patients with higher education and be reflected as reduced perfusion in the parietotemporal cortex. Therefore, in patients matched for overall severity of dementia, the parietotemporal flow deficit would be greater in those with more years of education.

Methods

Subjects

Fifty-eight consecutive patients with AD accepted into a longitudinal rCBF study provided informed consent for this

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study. Before rCBF measurement, all underwent extensive neurological and neuropsychological evaluations and met DSM-III-R criteria for dementia [16] and NINCDS-ADDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) criteria for probable Alzheimer's disease (pAD) [17]. Computed tomographic scanning or magnetic resonance imaging was used to rule out patients with vascular lesions or tumors. Electroencephalography, lumbar puncture, and laboratory tests (urinalysis, SMA20, complete blood cell count, B₁₂ levels, and thyroid function tests) were within normal limits. Psychiatric screening was used to assess the potential contribution of depression. Detailed, structured neurological and medical evaluation ruled out other neurological conditions. Neuropsychological evaluation included tests of memory (verbal and nonverbal, immediate and remote), language, visuospatial ability, abstract reasoning, general intellectual function (IQ), and praxis. Subjects with a history of prior neurological or psychiatric illness were excluded. There was no a priori selection of patients based on education, and rCBF played no role in the diagnostic process.

Procedures

CLINICAL MEASURES. Indices to assess the severity of the disease were administered separately from the neuropsychological battery administered to confirm diagnosis. The modified Mini-Mental Status Examination (mMMS) was used to estimate general intellectual function [18, 19]. This brief, 57-point scale tests memory, orientation, attention, language, and constructional abilities, and has established validity and reliability [20]. Change in the ability to perform day-to-day activities of daily living (ADL) also occurs in pAD and the degree of impairment in ADL can be independent of intellectual dysfunction [21]. The Blessed Dementia Rating Scale, Part 1 (BDRS) [22] was used to rate ADL. Duration of clinical symptoms and age at onset were estimated from an interview of the patient and all available informants.

rCBF. rCBF was measured as described elsewhere [10] with 32 scintillation detectors. All measurements were made under resting, supine conditions in a quiet, darkened room with weighted blinders placed over the subjects' eyes. Head positioning was maintained in relation to light markers aligned to the canthomeatal line. Extensive quality control standards were used [23]. Clearance curves were analyzed with a six-unknown model (M2) that provides greater sensitivity and accuracy under low-flow conditions [24]. We chose to use the initial slope index (ISI) derived from the model as the dependent variable because this index showed the best discrimination of AD and controls in a previous study [10]. ISI is a measure of cerebral blood flow dominated by gray matter but stabilized by white matter. This variable does not depend on partition coefficients, but corresponds to ml/100 gm/min if the blood-brain partition coefficient for Xe is assumed to be 1.0 in the tissue volume of interest.

Global perfusion was examined by using whole-cortex mean values. When examining regional flows at specific detectors, we eliminated general flow effects by computing a relative distribution value for each region consisting of normalization by the global mean flow for each subject. We also

calculated a parietal index, which consists of the sum of two parietal lobe detectors (P1 and P3) divided by the sum of two reference detectors (O2 and C1). This index is typically reduced in patients with AD, but not in controls or those with other dementing illnesses [10, 25].

At the time of rCBF, end tidal Pco₂ was assessed during the 11-minute rCBF measurement period. Blood pressure was obtained after the measurement.

Statistical Analysis

Patients were initially subdivided into 3 ranges of education, and global and regional flows were compared using analysis of variance (ANOVA). We first investigated the possibility of a systematic relation between lateralized flow measures and educational level by performing a 2 × 3 ANOVA, treating the right and left hemisphere values as repeated measures and investigating the interaction between hemisphere and education level. Because neither interactions nor main effects were significant, we averaged ISI values from right and left detectors, to simplify subsequent comparisons, which were made using one-way ANOVA.

Correlational analyses investigated the relation between education and rCBF. Stepwise multiple regression was used to estimate the variance of selected rCBF indices that is explained by education after controlling for other relevant clinical indices.

Results

Table 1 summarizes the demographic and clinical characteristics of the following three education groups: less than 12 years of education (range, 3–11 yr), high school graduate (12 yr), and greater than high school (range, 13–24 yr). Based on one-way ANOVA and χ^2 tests as appropriate, the three groups did not differ on any clinical measure or demographic characteristic assessed.

Both mean whole brain flow and the parietal index were low, consistent with previous reports in pAD [10, 23]. The values were inversely related to education, but did not differ significantly across groups (Table 2). However, exclusion of a single extreme outlier in the lowest education group yielded significant differences in the expected direction for the parietal index.

For each education group, percentage of flow relative to whole brain at individual detectors is illustrated in the Figure, and values that differed significantly across groups are summarized in Table 2. Significant differences were seen across the education groups at the following three detectors in the parietotemporal area: T3, P3, and O2. In each case, post hoc analyses revealed greater flow reduction in the highest education group relative to the other groups. The most pronounced decline in relative flow was noted at the P3 detector.

Correlation coefficients were calculated to investigate the relation between education, treated as a continuous variable, and percentage of flow at each de-

Table 1. Summary of Demographics and Clinical Measures for the Three Education Groups

	Mean (SD)			<i>p</i>
	Below HS	HS Graduate	Above HS	
n	18	18	22	...
Age (yr)	69.4 (10.3)	68.6 (11.2)	65.9 (8.1)	NS
Education (yr)	7.8 (2.6)	12.0 (0.0)	17.3 (3.1)	0.01
Age at onset (yr)	66.0 (10.0)	64.4 (11.2)	61.5 (9.4)	NS
Duration (yr)	4.1 (2.5)	4.0 (2.4)	4.5 (2.6)	NS
mMMS	29.7 (11.0)	28.3 (10.6)	32.8 (9.3)	NS
BDRS	9.5 (4.6)	9.5 (4.0)	10.3 (4.4)	NS
BP sys (mm Hg)	137.4 (19.9)	134.0 (16.2)	130.9 (15.0)	NS
BP dia (mm Hg)	76.4 (11.2)	76.7 (11.9)	74.2 (12.6)	NS
Pco ₂ (mm Hg)	36.6 (4.4)	36.7 (4.5)	37.4 (4.9)	NS
Non-white (%)	11.1	5.5	9.1	NS
Right handed (%)	72.2	88.8	90.9	NS
English, first language (%)	61.1	77.7	90.9	0.08
Female (%)	72.2	72.2	45.5	NS

HS = high school; mMMS = modified Mini-Mental Status examination; BDRS = Blessed Dementia Rating Scale; BP sys = systolic blood pressure; BP dia = diastolic blood pressure; Pco₂ = partial pressure carbon dioxide; NS = not significant.

Table 2. Summary of Cortical Perfusion Values for the Three Education Groups

	Mean (SD)			<i>p</i>
	Below HS	HS Graduate	Above HS	
n	18	18	22	...
Mean flow	43.5 (8.5)	42.2 (8.7)	39.3 (6.3)	NS
Parietal index	0.936 (0.064)	0.915 (0.054)	0.903 (0.051)	NS
F5	1.037 (0.053)	1.034 (0.033)	1.074 (0.048) ^a	0.02
T3	0.991 (0.057)	1.005 (0.043)	0.960 (0.066) ^b	0.05
P3	0.937 (0.06)	0.921 (0.053)	0.883 (0.046) ^a	0.01
O2	1.013 (0.044)	1.025 (0.034)	0.987 (0.03) ^a	0.01

Mean flow represents actual blood flow in initial slope index units. The remaining items are flows relative to reference areas (parietal index) or to global flow for individual detectors, and are averaged across right and left hemispheres. *p* values are for one-way analyses of variance with superscript letters summarizing follow-up pairwise comparisons.

^aDiffers significantly from both other groups.

^bDiffers significantly from the high school graduate group.

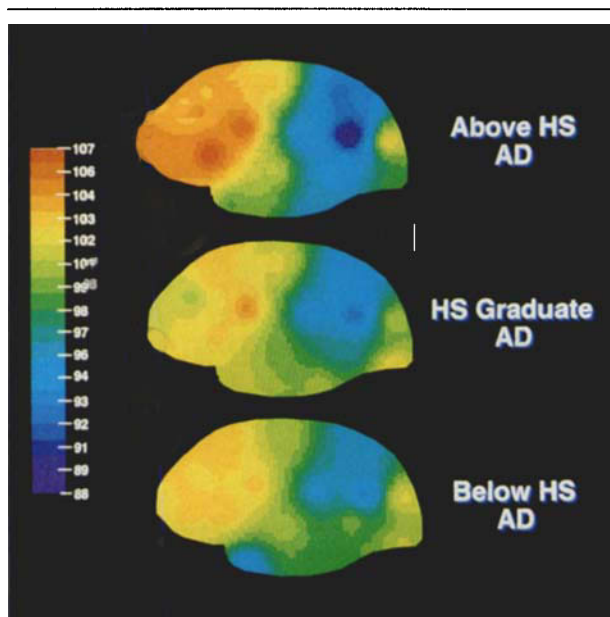
HS = high school; parietal index = flow in the parietal region (P1, P3 detectors) divided by perirolandic (C1) and occipital (O2) regions; NS = not significant.

tector. Significant negative correlations, suggesting reduced flow associated with more education, occurred at the O1 and P3 detectors ($r = -0.259$ and -0.361 , respectively, $p < 0.05$ for both). A significant positive correlation was observed at the F5 detector ($r = 0.299$, $p < 0.05$) with higher education associated with relatively increased flow, that is, less decreased than in other regions.

Because reduced flow at the P3 detector best discriminated AD patients and matched controls in a previous study [10], we explored the relation between education and flow at this detector using multiple linear regression. Using P3 percentage of flow as the dependent measure, we forced the following 4 variables that assess dementia severity into the regression model: mMMS, BDRS, age, and duration. The model ac-

counted for 15.1% of the variance in P3 flow. We then added education to the model to evaluate the increment in variance of P3 flow explained by education and 28.6% of the variance in P3 was explained, an increment of 13.5%. This significant increment ($F[1,51] = 9.46$, $p < 0.01$) suggests that after statistically controlling for variations in the clinical severity of dementia, education is strongly related to the reduction in flow at this detector.

A similar regression analysis was also calculated for the parietal index. Before including education, the severity measures accounted for 14.4% of the variance in the index. When education was added to the model, it accounted for 23.3% of the variance in the parietal index, a significant increase ($F[1,51] = 5.79$, $p < 0.05$).



Comparison of relative perfusion in the three educational level AD groups. Regional cerebral blood flow is expressed relative to global flow at each detector, averaged across right and left hemispheres. The high end of the color scale (i.e., red) indicates relatively higher cortical perfusion values expressed as a percentage of whole cortex mean initial slope index, whereas the low end of the scale (i.e., blue) represents lower flows relative to global mean perfusion. Note the relative reductions of perfusion in the parietotemporal region for all three AD groups with a markedly greater parietotemporal deficit among patients with above high school educations. HS = high school; AD = Alzheimer's disease.

Additional Analyses

The distribution of English as a first language was not significantly different across groups but approached significance. To evaluate the potential effects of this variable, all described analyses were recalculated, after stratifying by first language. In no case did first language status contribute any significant variance.

A separate group of 34 nondemented controls were also assessed with identical rCBF and clinical procedures. Education ranged from 8 to 18 years, but mean age was comparable with the pAD patients. There was no significant correlation between flow at any detector and education. Although range of education is truncated in the controls, it does include education levels whose flow differed significantly in the pAD patients. This suggests that the relation between education and flow is specific to the demented group.

Discussion

This study offers physiological evidence that education provides a reserve against the clinical expression of AD. Our rCBF data indicate an inverse relation between education and cerebral perfusion. Although

global perfusion, which is not specific to AD, was comparable across education groups, patients with more education had the greatest perfusion deficits in the area where flow reduction is specific to AD.

Interpretation of these findings relies on several assumptions. The first assumption is that years of education reflects cognitive capacity. Clearly not all individuals reach the level of educational attainment consistent with their potential, and the converse is also true. In addition, in this elderly group, expectations for education beyond high school might be subject to cohort effects where older subjects are less likely to complete higher education. Despite these considerations, a general relation between education and intellectual ability is a reasonable assumption. If a better measure of innate intellectual capacity were available, the relations observed here might be stronger. It is also possible that the experience of education itself provides a set of cognitive tools that allow the individual to compensate for the underlying pathological changes that occur as AD progresses.

A second assumption is that rCBF is an effective measure of the AD disease process. The sensitivity and specificity of the regional rCBF changes in AD has already been discussed. The precise cause of the flow defect is still unknown, but the distribution has considerable overlap with the cortical areas with the greatest density of histopathological abnormalities, including loss of large neurons, neuritic plaques, and neurofibrillary tangles [26–28]. The focal parietotemporal abnormality may well be related to a cholinergic deficit because nicotinic receptor blockade in normal subjects models it [29]. This functional lesion may also represent an anatomical lesion, that is, local neuronal loss. A unique case report by McGeer and colleagues [30] strongly implicated local necrosis and gliosis as the major determinant on focal glucose metabolism deficits in AD. Because the metabolic coupling of local perfusion is known to be intact in AD [31], rCBF may be considered to reflect neuronal integrity and synaptic activity of the cortex. Regardless of the specific index of degeneration used, overall estimates of local degeneration correlate well in their topographic distribution with rCBF [32]. It is therefore reasonable to assume that the flow reduction is an index of the physiological changes of AD.

This study does not indicate that education affords some type of immunity to the AD process. On the contrary, AD occurs independently of education. Rather, if we assume that level of education in some way reflects cognitive capacity or stores, then the present data suggest that this might delay the clinical manifestations of the AD. Dementia was not detected in the higher educated patients until functioning was impaired to the same degree as that in the lower education patients. Although estimates of duration of illness

since the onset of symptoms and functional incapacity are comparable across the three education groups, we propose that the AD was present longer in the patients with higher education, even though it was not clinically evident.

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